# Synthesis and Anti-HIV-1 Activity Evaluation of 5-Alkyl-2-alkylthio-6-(arylcarbonyl or α-cyanoarylmethyl)-3,4-dihydropyrimidin-4(3*H*)-ones as Novel Non-nucleoside HIV-1 Reverse Transcriptase Inhibitors

Lei Ji,[†] Fen-Er Chen,[†,*] Erik De Clercq,[‡] Jan Balzarini,[‡] and Christophe Pannecouque[‡]

*Department of Chemistry, Fudan University, Shanghai 200433, People's Republic of China, and Rega Institute for Medical Research, Katholieke Universiteit Leuven, 10 Minderbroedersstraat, B-3000 Leuven, Belgium*

*Received October 9, 2006*

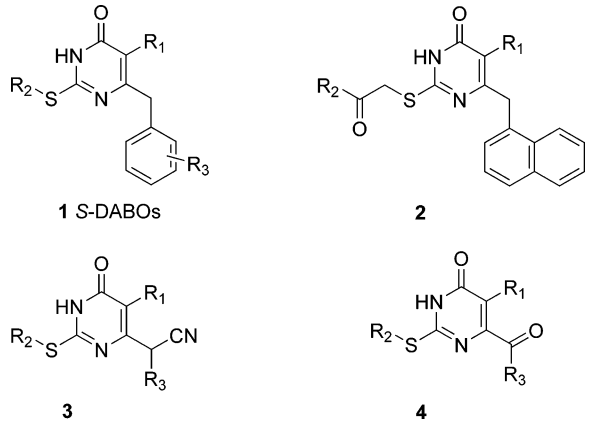
A series of novel *S*-DABO analogues (*S*-DABOs, **1**) were synthesized and evaluated as inhibitors of human immunodeficiency virus type-1 (HIV-1). Key structural modifications included replacement of the 6-arylmethyl group by a 6-arylcarbonyl or 6-(α-cyanoarylmethyl) group. Most of the compounds showed only micromolar potency against HIV-1 in MT-4 cells in vitro, though two of them (**3e** and **3g**) were unusually potent ($IC_{50}$ = 0.09 and 0.002 μM, respectively) and selective (SI = 1500 and 4600, respectively). Structure−activity relationships among the newly synthesized *S*-DABOs are discussed.

## Introduction

Since they were first reported in 1992,[1] 2-alkoxy-3,4-dihydro-6-benzyl-4(3*H*)-pyrimidin-4-ones (DABOs),[2−18] a class of non-nucleoside reverse transcriptase inhibitors (NNRTIs), have been the object of great interest and have led in recent years to the indentification of highly potent analogues in which the 6-benzyl group was replaced by a substituted arylmethyl group or the 2- and 5-substituent on the pyrimidine ring was variously modified as depicted in Chart 1. However, few modifications of the arylmethyl carbon at the 6-position have been described.[11] We recently prepared a series of new 6-(1-naphthylmethyl) analogues (**2,** Chart 1) which showed strong in vitro anti-HIV-1 and anti-HIV-2 activity in MT-4 cells, together with high selectivity for the retroviruses relative to the T-cell host.[19] Surmising that suitable modification of the $CH_2$ bridge between the pyrimidine and aryl moieties might promote π-stacking between the electron-deficient pyrimidine ring of the inhibitor and the electron-rich phenyl ring of Tyr188 or Tyr181 in the transcriptase enzyme, we have now synthesized and tested a new series of 6-(α-cyanoarylmethyl) and 6-aroyl analogues **3** and **4** (Chart 1) as novel NNRTIs.

**Chemistry.** The synthesis of the title compounds of series A (**3a**−**ac**) and series B (**4a**−**m**) was outlined in Scheme 1and Scheme 2. The 2-thiobarbituric acid derivatives **6a**−**d** were prepared according to the method of Koroniak et al.[20] by condensation of thiourea with the appropriate diethyl malonates **5a**−**d** in the presence of sodium methoxide in methanol at refluxing temperature. Subsequent S-alkylation of **6a**−**d** with various alkyl halides in the presence of sodium hydroxide gave the corresponding 5-alkyl-2-alkylthiobarbituric acids **7a**−**ac**, respectively. Treatment of **7a**−**ac** in dichloromethane with *p*-toluenesulfonyl chloride and triethylamine afforded the disulfonates **8a**−**ac**, which were reacted with various aryl acetonitriles in the presence of 60% NaH in anhydrous DMF to yield the intermediates **9a**−**ac**, respectively, and then without purification, hydrolysis of **9a**−**ac** with 10% aqueous sodium hydroxide in ethanol afforded the title compounds **3a**−**ac** of series A.

**Chart 1.** Chemical Structures of *S*-DABOs, and Compounds **2**−**4**




Besides, the nitriles **3b**, **3d**, **3g**, **3j,k**, **3m**, **3t**, and **3x**−**ac** were successfully oxidized to ketones **4a**−**m** (series B) by passing air through the reaction mixture in the presence of 60% NaH in anhydrous DMF at room temperature.

## Results and Discussion

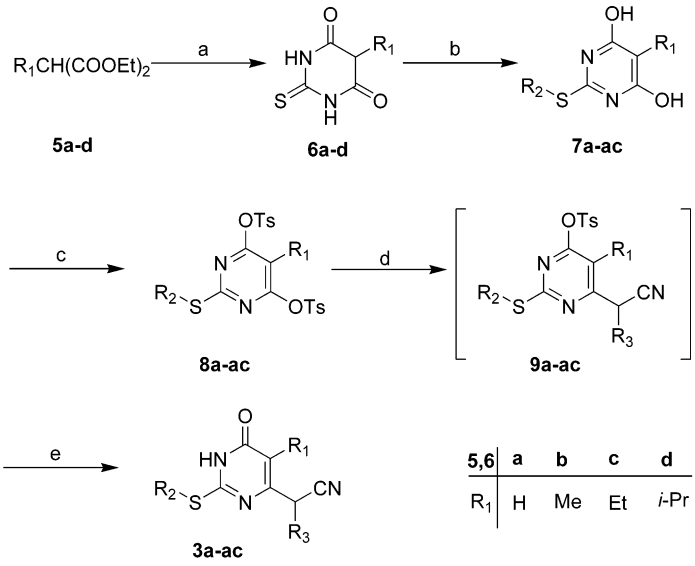
At the outset, the title compounds of series A (**3a**−**w**) and series B (**4a**−**m**) were tested for their ability to inhibit the HIV-1 induced cytopathogenicity, for cytotoxicity and anti-HIV-1 activity in MT-4 cells in comparison with nevirapine as reference drug (Table 1). In series A, many compounds showed anti-HIV-1 activity that was more potent than that of nevirapine. Maximum activity was obtained with compounds of **3e** and **3g**, which were endowed with the highest potency ($IC_{50}$ = 0.09 and 0.002 μM, respectively) and selectivity (SI = 1500 and 4600, respectively). These results appear to confirm our assumption that the introduction of a cyano group as an electron-withdrawing substituent to the aryl methylic carbon at C-6 position might be more favorable to improve a putative π-stacking interaction between the electron-deficient aryl ring of the ligand and the electron-rich benzene ring of Tyr188 or Tyr181 of reverse transcriptase (RT).

Compounds belonging to series B were considerably less potent (**4a**, **4g**−**i**, **4k**, and **4m**) or totally inactive (**4b**−**d**, **4f**, and **4j**). However, a striking low cytotoxicity in this series was

* To whom correspondence should be addressed. Tel: +86-21-65643811. Fax: +86-21-65643811. E-mail: rfchen@fudan.edu.cn.
[†] Fudan University.
[‡] Katholieke Universiteit Leuven.

10.1021/jm061167r CCC: $37.00 
Published on Web 03/24/2007

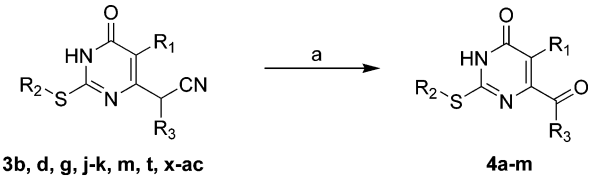
**Scheme 1**[a] Synthesis of Compounds **3a**−**ac**




| 3 | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|
| a | H | *i*-Pr | 1-naphthyl |
| b | H | cyclopentyl | 1-naphthyl |
| c | Me | cyclopentyl | 1-naphthyl |
| d | Me | propynyl | 1-naphthyl |
| e | Me | benzoylmethyl | 1-naphthyl |
| f | Me | 4-chlorobenzoylmethyl | 1-naphthyl |
| g | Me | *i*-Pr | Ph |
| h | Me | cyclopentyl | Ph |
| i | Me | benzoylmethyl | Ph |
| j | Et | Et | 1-naphthyl |
| k | Et | *i*-Pr | 1-naphthyl |
| l | Et | cyclopentyl | 1-naphthyl |
| m | Et | allyl | 1-naphthyl |
| n | Et | propynyl | 1-naphthyl |
| o | Et | 4-nitrobenzyl | 1-naphthyl |
| p | Et | 4-chlorobenzoylmethyl | 1-naphthyl |
| q | Et | *i*-Pr | Ph |
| r | Et | 4-nitrobenzyl | Ph |
| s | Et | 4-nitrobenzyl | 2,6-$Cl_2$-Ph |
| t | *i*-Pr | cyclopentyl | 1-naphthyl |
| u | *i*-Pr | 4-methoxybenzyl | 1-naphthyl |
| v | *i*-Pr | 4-methoxybenzyl | Ph |
| w | *i*-Pr | 4-methoxybenzyl | 2,6-$Cl_2$-Ph |
| x | H | Et | 1-naphthyl |
| y | H | Et | Ph |
| z | H | benzoylmethyl | 1-naphthyl |
| aa | Et | benzyl | 1-naphthyl |
| ab | Et | benzyl | 2-naphthyl |
| ac | Et | cyclopentyl | Ph |

[a] Reagents and conditions: (a) thiourea, MeONa, MeOH, reflux, 8 h; (b) $R_2X$, NaOH, $H_2O$, 35 °C, 4−24 h; (c) TsCl, $Et_3N$, $CH_2Cl_2$, −5 °C then rt, overnight; (d) $R_3CHCN$, 60% NaH, DMF, −15 °C then rt, 48−72 h; (e) 10% NaOH, EtOH, rt, 24−48 h.

**Scheme 2**[a] Synthesis of Compounds **4a**−**m**



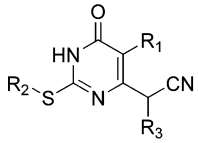

| 4 | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|
| a | H | Et | 1-naphthyl |
| b | H | cyclopentyl | 1-naphthyl |
| c | H | benzoylmethyl | 1-naphthyl |
| d | H | Et | Ph |
| e | Me | *i*-Pr | Ph |
| f | Me | propynyl | 1-naphthyl |
| g | Et | Et | 1-naphthyl |
| h | Et | *i*-Pr | 1-naphthyl |
| i | Et | allyl | 1-naphthyl |
| j | Et | benzyl | 1-naphthyl |
| k | Et | benzyl | 2-naphthyl |
| l | Et | cyclopentyl | Ph |
| m | *i*-Pr | cyclopentyl | 1-naphthyl |

[a] Reagents and conditions: (a) 60% NaH, DMF, Air, rt, 6−12 h.

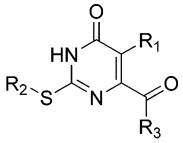
observed. For example, the majority of compounds were not cytotoxic for MT-4 cells at doses as high as 120 $\mu$M, and only two of them (**4b** and **4m**) showed $CC_{50}$ values at concentrations lower than 30 $\mu$M. Inspired by these observations further structural modifications at positions 2, 5, and 6 were performed. Two compounds (**4e** and **4l**) were found to exhibit moderate activity. It was noteworthy that the introduction of a 6-arylcarbonyl substituent resulted in compounds of series B, which were characterized by lower activity but coupled with marked decrease in cytotoxicity. It was anticipated that this may be due to the increase of molecule rigidity resulting in a steric clash with adjacent residues that weaken interaction with the RT.

In an attempt to further study the SARs, we examined the effect of $R_3$ substituents at C-6 position of the pyrimidine ring by use of various aryl groups. It can be seen that 1-naphthyl-substituted compounds (**3c**, **3k**, and **3o**) were generally more potent than the phenyl-substituted compounds (**3h**, **3q**,**r**) with the exception of the pair **3v** and **3u** in series A. In line with these observations, a similar conclusion was reached about series B. These results indicated that the 1-naphthyl substitution of $R_3$ was more favorably positioned to make interactions with the $\pi$-clouds of the aromatic chain of Tyr181 or Tyr188 of RT may be due to the higher aromatic properties and bulky steric hindrance. It was previously reported that in other *S*-DABO series the insertion of two chlorine atoms at the ortho-position of phenyl ring at C-6 position strongly improved the anti-HIV-1 activity.[18] For compounds **3**, we were also testing the effect of changing $R_3$ = phenyl into $R_3$ = 2,6-dichlorophenyl. The effect was rather dramatic as can be seen by comparing **3v** with **3w** with a decrease in activity against HIV-1. A similar change in

**Table 1.** Anti-HIV-1 Activity and Cytotoxicity of Compounds **3a**−**w, 4a**−**m** in MT-4 Cells



**3a-w**



**4a-m**

| compd | $R_1$ | $R_2$ | $R_3$ | $IC_{50}$ ($\mu$M)[a] | $CC_{50}$ ($\mu$M)[b] | SI[c] |
|---|---|---|---|---|---|---|
| **3a** | H | *i*-Pr | 1-naphthyl | 0.66 ± 0.27 | 53.19 ± 20.72 | 82 |
| **3b** | H | cyclopentyl | 1-naphthyl | >22.80 | 22.80 ± 4.52 | <1 |
| **3c** | Me | cyclopentyl | 1-naphthyl | 0.80 ± 0.40 | 49.39 ± 21.49 | 61 |
| **3d** | Me | propynyl | 1-naphthyl | 2.70 ± 1.16 | 46.09 ± 1.54 | 17 |
| **3e** | Me | benzoylmethyl | 1-naphthyl | 0.09 ± 0.04 | 163.86 ± 33.16 | 1500 |
| **3f** | Me | 4-chlorobenzoylmethyl | 1-naphthyl | 4.71 ± 0.89 | 148.32 ± 21.24 | 32 |
| **3g** | Me | *i*-Pr | Ph | 0.002 ± 0.0002 | 10.81 ± 6.56 | 4600 |
| **3h** | Me | cyclopentyl | Ph | 6.34 ± 2.09 | 58.95 ± 15.48 | 9 |
| **3i** | Me | benzoylmethyl | Ph | 7.28 ± 3.17 | 53.81 ± 13.76 | 7 |
| **3j** | Et | Et | 1-naphthyl | 1.17 ± 0.23 | 122.35 ± 63.98 | 103 |
| **3k** | Et | *i*-Pr | 1-naphthyl | 0.24 ± 0.12 | >344.35 | >1400 |
| **3l** | Et | cyclopentyl | 1-naphthyl | 0.18 ± 0.08 | 51.88 ± 18.33 | 293 |
| **3m** | Et | allyl | 1-naphthyl | 0.58 ± 0.33 | >346.26 | >585 |
| **3n** | Et | propynyl | 1-naphthyl | 4.85 ± 0.61 | 47.99 ± 9.50 | 10 |
| **3o** | Et | 4-nitrobenzyl | 1-naphthyl | 1.25 ± 0.07 | 24.52 ± 1.38 | 20 |
| **3p** | Et | 4-chlorobenzoylmethyl | 1-naphthyl | ≥35.73 | 116.66 ± 13.07 | ≤3 |
| **3q** | Et | *i*-Pr | Ph | 0.64 ± 0.38 | 58.02 ± 21.02 | 91 |
| **3r** | Et | 4-nitrobenzyl | Ph | 1.33 ± 0.27 | 34.19 ± 2.14 | 26 |
| **3s** | Et | 4-nitrobenzyl | 2,6-$Cl_2$-Ph | 2.22 ± 0.44 | 23.46 ± 2.83 | 11 |
| **3t** | *i*-Pr | cyclopentyl | 1-naphthyl | 1.34 ± 0.38 | 7.32 ± 1.09 | 5 |
| **3u** | *i*-Pr | 4-methoxybenzyl | 1-naphthyl | >2.09 | 2.09 ± 1.47 | <1 |
| **3v** | *i*-Pr | 4-methoxybenzyl | Ph | 3.53 ± 0.81 | 26.79 ± 2.72 | 8 |
| **3w** | *i*-Pr | 4-methoxybenzyl | 2,6-$Cl_2$-Ph | >23.53 | 23.53 ± 1.31 | <1 |
| **4a** | H | Et | 1-naphthyl | 37.58 ± 3.87 | 241.61 ± 13.61 | 6 |
| **4b** | H | cyclopentyl | 1-naphthyl | >21.03 | 21.03 ± 9.80 | <1 |
| **4c** | H | benzoylmethyl | 1-naphthyl | >304.41 | >304.41 | NA |
| **4d** | H | Et | Ph | >246.65 | 246.65 ± 19.46 | <1 |
| **4e** | Me | *i*-Pr | Ph | 2.05 ± 0.03 | 263.19 ± 27.08 | 128 |
| **4f** | Me | propynyl | 1-naphthyl | >123.56 | 123.56 ± 35.57 | <1 |
| **4g** | Et | Et | 1-naphthyl | 27.84 ± 9.17 | 196.54 ± 112.37 | 7 |
| **4h** | Et | *i*-Pr | 1-naphthyl | 6.79 ± 0.51 | 178.92 ± 16.59 | 26 |
| **4i** | Et | allyl | 1-naphthyl | 16.94 ± 8.40 | 210.37 ± 54.09 | 12 |
| **4j** | Et | benzyl | 1-naphthyl | >312.50 | >312.50 | NA |
| **4k** | Et | benzyl | 2-naphthyl | ≥60.75 | 157.43 ± 7.73 | ≤3 |
| **4l** | Et | cyclopentyl | Ph | 4.69 ± 1.31 | 60.37 ± 17.19 | 13 |
| **4m** | *i*-Pr | cyclopentyl | 1-naphthyl | 10.87 ± 2.24 | 24.69 ± 2.86 | 2 |
| HEPT | | | | 5.06 | 405 | 80 |
| nevirapine | | | | 0.25 | >200 | >800 |

[a] $IC_{50}$: concentration of compound required to protect the cell against viral cytopathogenicity by 50% in MT-4 cells. [b] $CC_{50}$: concentration of compound that reduces the normal uninfected MT-4 cell viability by 50%. [c] SI: selectivity index: ratio $CC_{50}/IC_{50}$.

activity was observed for compound **3r** ($IC_{50}$ = 1.33 ± 0.27 $\mu$M) when compared with **3s** ($IC_{50}$ = 2.22 ± 0.44 $\mu$M). The results in our case suggested that the substituent at $R_3$ is an important criterion for activity.

Variations at the C-5 position of pyrimidine ring play an important role, as previously observed,[9,19] and allow compounds with very high potent activity to be obtained. None of the modifications at the C-5 position proved to be devoid of anti-HIV-1 activity or less potent than the 5-methyl-substituted compounds. However, it also should be noticed that except for compounds **3c** and **3l**, substitutions of the 5-methyl with either ethyl or the isopropyl resulted in slightly decreased activity (from **3c,d** to **3t** and **3n**, respectively) or markedly decreased activity (up to 7-fold passing from **3f** to **3p**). Thus, within the derivatives in series A, the best activity was provided by the 5-methyl-substituted derivative. For example, compounds **3c**, **3e**, and **3g** containing 5-methyl substitution displayed high potency with $IC_{50}$ values ranging from 0.80 to 0.002 $\mu$M.

Just as with SARs of our previous *S*-DABOs,[19] the nature of the substituents at C-2 position were also essential for the anti-HIV-1 activity both in series A and B. As shown in Table 1, steric properties of the substituents at the C-2 position of pyrimidine ring affected the antiviral activity as exemplified by 4-fold improvement of activity passing from the 2-ethylthio homologues **3j** and **4g** to the corresponding 2-isopropylthio analogues **3k** and **4h**. Optimal activity was obtained with compounds bearing such 2-alkylthio substituents as isopropylthio, cyclopentylthio, allylthio, and benzoylmethylthio groups. Among these serial modifications, the 2-isopropylthio-substituted compounds of series A generally showed the best potency with $IC_{50}$ values in the low nanomolar or sub-micromolar range. The introduction of an allylthio moiety at the C-2 position gave compound **3m**, which displayed sub-micromolar anti-HIV-1 activity with the lowest cytotoxicity ($IC_{50}$ = 0.58 $\mu$M, $CC_{50}$ > 346.26 $\mu$M). It is worth noting that the insertion of a chlorine atom at the para-position of the benzoylmethyl ring led to compounds **3f** and **3p** characterized by both low cytotoxicity and antiviral activity.

In addition, we have chosen two compounds (**3e** and **3k)** to evaluate their anti-HIV-1 activity in human peripheral blood mononuclear cells (PBMCs) (Figure 3, Table 2). It was found that these two compounds showed moderate anti-HIV-1 activity in human PBMCs. In particular, compound **3e** exhibited low micromolar value of $IC_{50}$ of 0.99 $\mu$M. However, in comparison

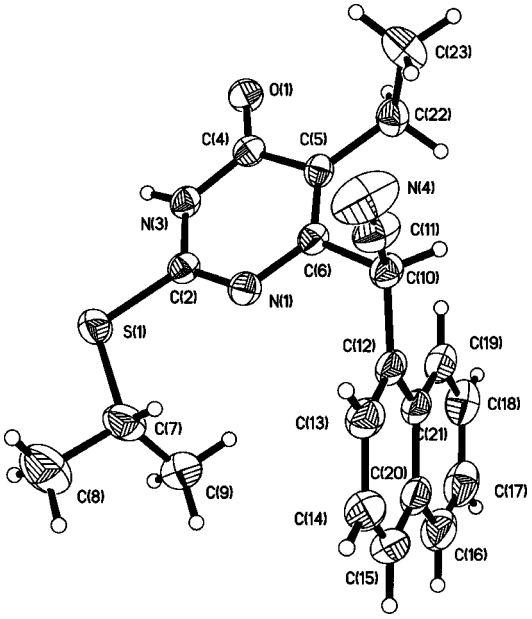



**Figure 1.** Crystal structure of compound **3k**.

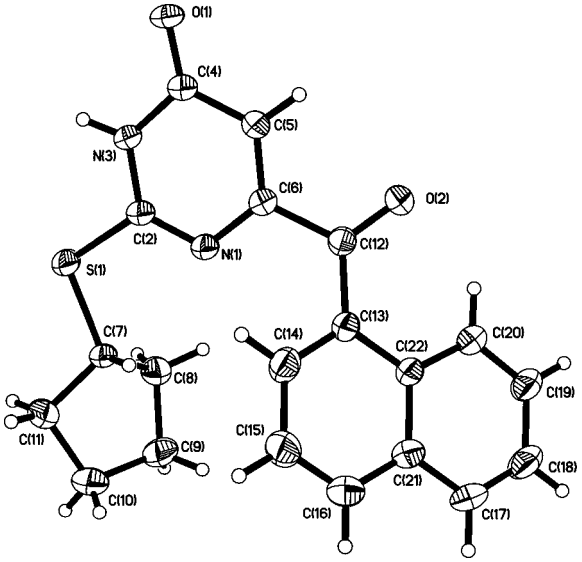



**Figure 2.** Crystal structure of compound **4b**.

with the MT-4 cell line, this cell line appears to be less sensitive. These two compounds proved to be approximately 7 to 10-fold less active in PBMCs than in MT-4 cells. The decreased anti-HIV-1 activities were also coupled with increased cytotoxicity in PBMCs. The SI values decreased by about 20- to 30-fold for the two compounds.

**Molecular Modeling Analysis.** With the aim to investigate the binding mode of our newly synthesized compounds, a modeling study was performed by means of AutoDock for docking. Compound **3g** was chosen to be docked into the non-nucleoside binding site (NNBS) of HIV-1 RT. Coordinates of the NNBS were taken from the crystal structure of the RT/6-benzyl-1-(ethoxymethyl)-5-isopropyluracil (MKC-442) complex due to the high degree of similarity between MKC-442 and DABOs. The theoretical binding mode of **3g** to the NNBS is shown in Figure 4.

Results showed that the pyrimidine NH moiety at position 3 was engaged in a hydrogen bond with the C═O moiety of Lys101. The 6-(α-cyanobenzyl) moiety of **3g** fits into the aromatic-rich non-nucleoside binding pocket (NNBP), surrounded by the aromatic side chains of Tyr181, Tyr188, Phe227,

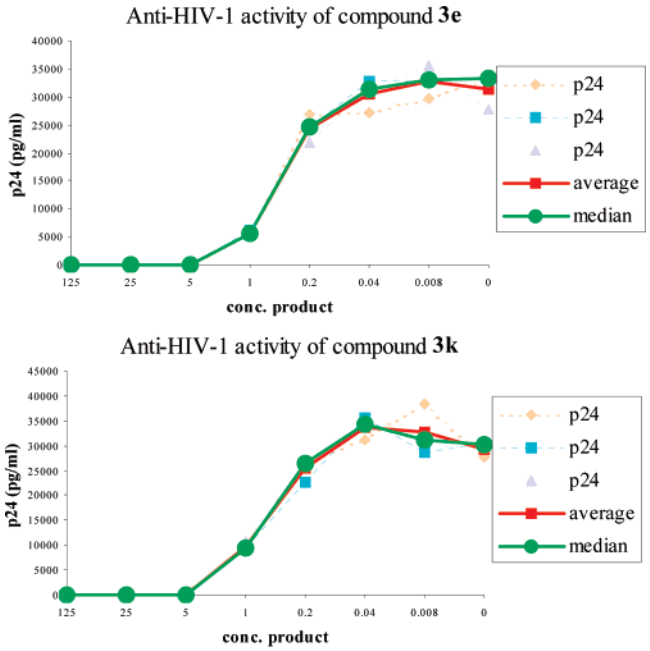



**Figure 3.** Anti-HIV-1 evaluation in PBMCs of selected compounds **3e** and **3k**.

**Table 2.** Anti-HIV-1 Activity and Cytotoxicity of Selected Title Compounds (**3e** and **3k)** in PBMCs

| compd | $IC_{50}$ ($\mu$M)[a] | $CC_{50}$ ($\mu$M)[b] | SI[c] |
|---|---|---|---|
| **3e** | 0.99 | 69.91 | 70 |
| **3k** | 1.66 | >68.87 | >41 |

[a] $IC_{50}$: concentration of compound required to achieve 50% reduction of p24 production in HIV-1 ($III_B$) infected PBMCs. [b] $CC_{50}$: concentration of compound that reduces the viability of mock-infected cells by 50%. [c] SI: selectivity index: ratio $CC_{50}/IC_{50}$.

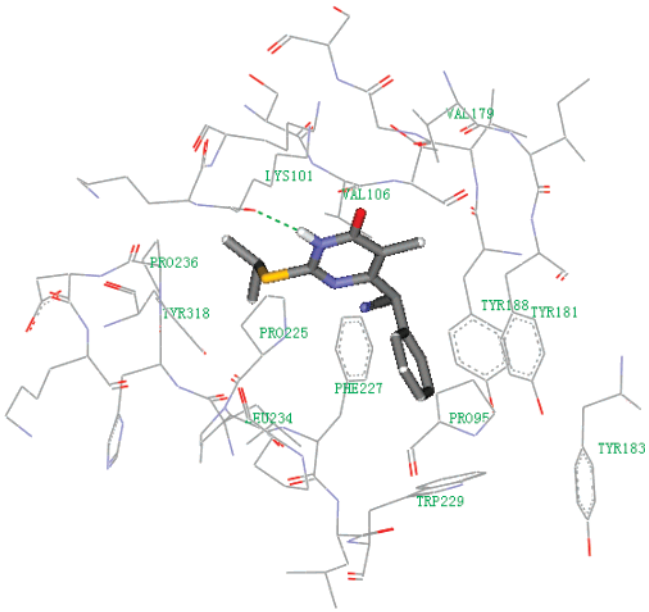



**Figure 4.** Model of **3g** docked into the RT non-nucleoside binding site. Putative intermolecular hydrogen bonds are highlighted by dashed lines.

and Trp229 as well as by Leu234 and Pro95. In particular, the phenyl ring interacts favorably with the Tyr181 side chain, giving rise to a positive $\pi$-stacking interaction. The 2-isopropylthio substituent was well accommodated in the Pro236 pocket. Moreover, the methyl group at C-5 position was

positioned in the hydrophobic cavity formed by the Val179 and Val106 side chains.

In summary, the results of the AutoDocking analysis supported our newly designed and synthesized compounds. Further optimization of **3g** will consider these aspects in further design attempts.

## Conclusion

In recent years much effort has been made to exploit novel and potent *S*-DABOs mainly through the modification of C-2, C-5, or the aryl ring of the C-6 moiety. Relatively little attention has been paid to modify the aryl methylic carbon bound to C-6 of the pyrimidine ring. Our structure-based design has led to the discovery that the introduction of a cyano at the aryl methylic carbon generated a series of novel S-DABO derivatives as a novel class of highly potent NNRTIs coupled with remarkable activity and high selectivity. And replacement of the 6-arylmethyl with a 6-arylcarbonyl led to compounds endowed with low cytotoxicity. The application of this novel and potent structure modification is expected to provide the foundation for the rational modification of the C-6 position and accelerate the discovery of more potent and selective NNRTIs.

## Experimental Section

**Chemistry.** Melting points were measured on a WRS-1 digital melting point apparatus and are uncorrected. Infrared (IR) spectra (KBr) were recorded on a Jasco FT/IR-4200 instrument. $^1$H NMR on a Bruker DMX 500 MHz or a Bruker AV 400 MHz spectrometer and $^{13}$C NMR spectra on a Bruker AV 400 MHz spectrometer were recorded in DMSO-$d_6$ or $CDCl_3$. Chemical shifts are reported in $\delta$ (ppm) units relative to the internal standard tetramethylsilane (TMS). Mass spectra were obtained on a Agilent MS/5975 mass spectrometer. Elemental analyses were performed on a CARLOERBA 1106 instrument, and the results of elemental analyses for C, H, Cl, N and S were within ±0.4% of the theoretical values. All chemicals and solvents used were of reagent grade and were purified and dried by standard methods before use. All air-sensitive reactions were run under a nitrogen atmosphere. All the reaction were monitored by TLC on pre-coated silica gel G plates at 254 nm under a UV lamp using ethyl acetate/hexane as eluents. Flash chromatography separations were obtained on silica gel (300−400 mesh).

**General Procedure for the Synthesis of 5-Alkyl-2-alkylthiobarbituric Acid Derivatives 7a−ac.** To a suspension of 5-alkyl-2-thiobarbituric acids **6a−d** (200 mmol) in water (500 mL) was added NaOH (8.0 g, 200 mmol) portionwise at room temperature. After the reaction mixture was stirred for 30 min, the appropriate alkyl halide (220 mmol) was added. Then the reaction mixture was stirred at room temperature for 4−24 h. The precipitate which formed was filtered off, washed with water, and dried to give **7a−ac** to be used in the next step without further purification.

**General Procedure for the Synthesis of the Disulfonates 8a−ac.** To a suspension of **7a−ac** (100 mmol) in anhydrous $CH_2Cl_2$ (500 mL) was added $Et_3N$ (181.8 g, 1800 mmol) at room temperature under a nitrogen atmosphere. After the mixture was stirred for 0.5 h and then cooled to −5 °C, a solution of TsCl (40.11 g, 210 mmol) in anhydrous $CH_2Cl_2$ (100 mL) was added dropwise. The whole was then stirred for 1 h, warmed to room temperature, and stirred overnight. After the resulting mixture was diluted with ice−water, the organic layer was separated and the aqueous was extracted with $CH_2Cl_2$. The combined organic phases were washed with 1% HCl and water, dried, and then concentrated in vacuo to afford the crude product to be used in the next step without further purification.

**General Procedure for the Synthesis of 5-Alkyl-2-alkylthio-6-(α-cyanoarylmethyl)-3,4-dihydropyrimidin-4(3*H*)-ones 3a−ac.** To a solution of **8a−ac** (20 mmol) in anhydrous DMF (100 mL) was added appropriate aryl acetonitriles (22 mmol) at room temperature. After the mixture was stirred for 0.5 h, 60% NaH (1.0 g, 24 mmol) was added portionwise at −10 °C under a nitrogen atmosphere. The whole was stirred at the same temperature for 1 h, warmed to room temperature, and then reacted for 48−72 h. The resulting mixture was acidified with acetic acid under ice-cooling and concentrated under reduced pressure to afford the crude intermediate **9a−ac**. Then without further purification, EtOH (300 mL) was added at room temperature. After the mixture was stirred for 0.5 h, 10% NaOH (100 mL) was added dropwise under ice-cooling. The reaction mixture was then stirred at room temperature for 24−48 h and then acidified to pH 5−6 with acetic acid. After most of the solvent was removed under reduced pressure, the resulting residue was poured into water and extracted with $CH_2Cl_2$. The organic layer was dried over $Na_2SO_4$ and concentrated in vacuo to give the crude product, which was first purified by flash chromatography (eluent: $CH_2Cl_2$) and followed by recrystallization from MeOH or AcOEt with the exception of compounds **3x−ac**, which were pure enough to be used in the next step without recrystallization.

**6-[α-Cyano-(1-naphthylmethyl)]-3,4-dihydro-2-isopropylthiopyrimidin-4(3*H*)-one (3a).** Yield 30.5%; recrystallized from AcOEt, mp 165.5−166.9 °C; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$ 1.19 (d, $J$ = 6.7 Hz, 3H, $CH_3$CH), 1.24 (d, $J$ = 6.7 Hz, 3H, $CH_3$-CH), 3.72 (sep, $J$ = 6.7 Hz, 1H, SCH), 6.19 (s, 1H, CHCN), 6.40 (s, 1H, CH), 7.57−8.25 (m, 7H, Naph), 12.87 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 400 MHz) $\delta$ 22.16 ($CH_3$), 22.30 ($CH_3$), 35.98 ($SCH_2$), 36.80 (CHCN), 107.33 (C5), 118.79 (CN), 123.37, 125.51, 126.23, 126.86, 127.40, 128.85, 129.31, 129.49, 129.97, 133.59 (Naph), 159.90 (C6), 160.29 (C2), 162.90 (C4); MS (EI) *m*/*z* 335 ($M^+$). Anal. ($C_{19}H_{17}N_3OS$) C, H, N, S.

**6-[α-Cyano-(1-naphthylmethyl)]-2-cyclopentylthio-3,4-dihydropyrimidin-4(3*H*)-one (3b).** Yield 42.1%; recrystallized from AcOEt, mp 185.7−187.0 °C; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$ 1.28−1.32 (m, 4H, cyclopentyl), 1.47 (m, 2H, cyclopentyl), 1.63 (m, 2H, cyclopentyl), 3.32−3.33 (m, 1H, cyclopentyl), 6.57 (s, 1H, CHCN), 6.62 (s, 1H, CH), 7.61−8.20 (m, 7H, Naph), 13.11 (s, 1H, NH); MS (EI) *m*/*z* 361 ($M^+$). Anal. ($C_{21}H_{19}N_3OS$) C, H, N, S.

**6-[α-Cyano-(1-naphthylmethyl)]-2-cyclopentylthio-3,4-dihydro-5-methylpyrimidin-4(3*H*)-one (3c).** Yield 43.9%; recrystallized from AcOEt, mp 214.1−215.0 °C; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$ 1.29−1.36 (m, 4H, cyclopentyl), 1.49 (m, 2H, cyclopentyl), 1.70 (m, 2H, cyclopentyl), 1.95 (s, 3H, $CH_3$), 3.47−3.50 (m, 1H, cyclopentyl), 6.52 (s, 1H, CHCN), 7.57−8.71 (m, 7H, Naph), 12.96 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 400 MHz) $\delta$ 10.63 ($CH_3$), 24.08 (2C, cyclopentyl), 24.22 (CHCN), 32.26 (2C, cyclopentyl), 43.32 (cyclopentyl), 118.63 (CN), 123.07, 124.79, 124.95, 126.56, 128.38, 128.72, 130.15, 132.05, 132.20, 133.37, 133.79 (Naph, C5), 156.07 (C6), 158.88 (C2), 163.30 (C4); MS (EI) *m*/*z* 375 ($M^+$). Anal. ($C_{22}H_{21}N_3OS$) C, H, N, S.

**6-[α-Cyano-(1-naphthylmethyl)]-3,4-dihydro-5-methyl-2-propynylthiopyrimidin-4(3*H*)-one (3d).** Yield 47.1%; recrystallized from MeOH, mp 218.4−218.9 °C; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$ 1.84 (s, 3H, $CH_3$), 3.19 (s, 1H, ≡CH), 3.89−4.01 (m, 2H, $SCH_2$), 6.53 (s, 1H, CHCN), 7.54−8.28 (m, 7H, Naph), 13.06 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 400 MHz) $\delta$ 10.09 ($CH_3$), 18.39 ($SCH_2$), 38.28 (CHCN), 73.43 (≡CH), 79.60 (≡C), 118.45 (CN), 123.03, 125.58, 126.26, 127.05, 127.08, 128.47, 128.93, 129.19, 129.68, 130.08, 133.55 (Naph, C5), 155.03 (C6), 157.44 (C2), 163.33 (C4); MS (EI) *m*/*z* 345 ($M^+$). Anal. ($C_{20}H_{15}N_3OS$) C, H, N, S.

**2-Benzoylmethylthio-6-[α-cyano-(1-naphthylmethyl)]-3,4-dihydro-5-methylpyrimidin-4(3*H*)-one (3e).** Yield 33.0%; recrystallized from MeOH, mp 195.6−196.8 °C; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$ 1.87 (s, 3H, $CH_3$), 4.76 (s, 2H, $SCH_2$), 6.44 (s, 1H, CHCN), 7.34−8.03 (m, 12H, Naph, Ph), 13.10 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 400 MHz) $\delta$ 11.02 ($CH_3$), 37.08 ($SCH_2$), 39.11 (CHCN), 117.39 (CN), 127.98 (2C), 128.69 (2C), 128.85, 128.97, 129.34, 129.96, 131.55, 133.55, 133.93, 134.18, 134.94, 135.07, 135.23, 135.69, 136.17 (Naph, Ph, C5), 156.03 (C6), 158.44 (C2), 163.26 (C4), 193.99 (C═O); MS (EI) *m*/*z* 425 ($M^+$). Anal. ($C_{25}H_{19}N_3O_2S$) C, H, N, S.

**2-(4-Chlorobenzoylmethylthio)-6-[α-cyano-(1-naphthylmethyl)]-3,4-dihydro-5-methylpyrimidin-4(3*H*)-one (3f).** Yield 35.9%;

recrystallized from MeOH, mp 176.7−177.9 °C; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$ 1.89 (s, 3H, $CH_3$), 4.69 (s, 2H, $SCH_2$), 6.51 (s, 1H, CHCN), 7.39−8.07 (m, 11H, Naph, Ph), 13.03 (s, 1H, NH); MS (EI) *m*/*z* 459 ($M^+$). Anal. ($C_{25}H_{18}ClN_3O_2S$) C, H, Cl, N, S.

**6-(α-Cyanobenzyl)-3,4-dihydro-2-isopropylthio-5-methylpyrimidin-4(3*H*)-one (3g).** Yield 44.5%; recrystallized from AcOEt, mp 161.6−163.4 °C; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$ 1.29 (d, $J$ = 6.8 Hz, 3H, $CH_3CH$), 1.42 (d, $J$ = 6.8 Hz, 3H, $CH_3CH$), 1.98 (s, 3H, $CH_3$), 3.87 (sep, $J$ = 6.8 Hz, 1H, SCH), 5.87 (s, 1H, CHCN), 7.35−7.46 (m, 5H, Ph), 12.80 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 400 MHz) $\delta$ 10.10 ($CH_3$), 22.39 ($CH_3CH$), 22.49 ($CH_3CH$), 36.11 (SCH), 40.36 (CHCN), 118.83 (CN), 127.72 (2C), 128.25, 129.02 (2C), 129.33, 134.22 (Ph, C5), 154.75 (C6), 158.10 (C2), 162.92 (C4); MS (EI) *m*/*z* 299 ($M^+$). Anal. ($C_{16}H_{17}N_3OS$) C, H, N, S.

**6-(α-Cyanobenzyl)-2-cyclopentylthio-3,4-dihydro-5-methylpyrimidin-4(3*H*)-one (3h).** Yield 39.9%; recrystallized from AcOEt, mp 168.2−169.1 °C; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$ 1.46−1.50 (m, 4H, cyclopentyl), 1.57−1.60 (m, 2H, cyclopentyl), 1.68−1.70 (m, 2H, cyclopentyl), 1.80 (s, 3H, $CH_3$), 3.74−3.75 (m, 1H, cyclopentyl), 5.34 (s, 1H, CHCN), 7.55−7.89 (m, 7H, Ph), 12.81 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 400 MHz) $\delta$ 10.54 ($CH_3$), 23.38 (CHCN), 24.26, 24.35 (cyclopentyl), 32.64, 32.81 (cyclopentyl), 43.03 (cyclopentyl), 116.49 (CN), 127.76, 128.87, 129.00, 129.72, 134.23, 134.46 (Ph, C5), 155.93 (C6), 159.34 (C2), 162.94 (C4); MS (EI) *m*/*z* 325 ($M^+$). Anal. ($C_{18}H_{19}N_3OS$) C, H, N, S.

**2-Benzoylmethylthio-6-(α-cyanobenzyl)-3,4-dihydro-5-methylpyrimidin-4(3*H*)-one (3i).** Yield 37.6%; recrystallized from MeOH, mp 156.0−157.6 °C; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$ 1.95 (s, 3H, $CH_3$), 4.75 (s, 2H, $SCH_2$), 6.56 (s, 1H, CHCN), 7.39−8.11 (m, 10H, Ph, Ph), 13.01 (s, 1H, NH); MS (EI) *m*/*z* 375 ($M^+$). Anal. ($C_{21}H_{17}N_3O_2S$) C, H, N, S.

**6-[α-Cyano-(1-naphthylmethyl)]-3,4-dihydro-5-ethyl-2-ethylthiopyrimidin-4(3*H*)-one (3j).** Yield 53.6%; recrystallized from AcOEt, mp 189.0−190.1 °C; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.99 (d, $J$ = 7.1 Hz, 6H, 2×$CH_3$), 2.33 (q, $J$ = 7.1 Hz, 2H, $CH_2CH_3$), 2.85 (q, $J$ = 7.1 Hz, 2H, $SCH_2$), 6.06 (s, 1H, CHCN), 7.59−8.89 (m, 7H, Naph), 13.03 (s, 1H, NH); MS (EI) *m*/*z* 349 ($M^+$). Anal. ($C_{20}H_{19}N_3OS$) C, H, N, S.

**6-[α-Cyano-(1-naphthylmethyl)]-3,4-dihydro-5-ethyl-2-isopropylthiopyrimidin-4(3*H*)-one (3k).** Yield 51.9%; recrystallized from AcOEt, mp 228.0−229.4 °C; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.77 (t, $J$ = 7.2 Hz, 3H, $CH_2CH_3$), 1.10 (d, $J$ = 6.7 Hz, 3H, $CH_3CH$), 1.33 (d, $J$ = 6.7 Hz, 3H, $CH_3CH$), 2.43 (q, $J$ = 7.2 Hz, 2H, $CH_2CH_3$), 3.69 (sep, $J$ = 6.7 Hz, 1H, SCH), 6.55 (s, 1H, CHCN), 7.55−8.18 (m, 7H, Naph), 12.85 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 400 MHz) $\delta$ 12.16 ($CH_2CH_3$), 18.33 ($CH_2CH_3$), 22.27 ($CH_3CH$), 22.42 ($CH_3CH$), 36.08 (CHCN), 38.07 (SCH), 118.87 (CN), 122.42, 123.04, 125.52, 126.20, 126.87, 126.92, 128.88, 129.08, 130.02, 130.38, 133.54 (Naph, C5), 154.16 (C6), 158.29 (C2), 162.50 (C4); MS (EI) *m*/*z* 363 ($M^+$). Anal. ($C_{21}H_{21}N_3OS$) C, H, N, S.

**6-[α-Cyano-(1-naphthylmethyl)]-2-cyclopentylthio-3,4-dihydro-5-ethylpyrimidin-4(3*H*)-one (3l).** Yield 44.4%; recrystallized from AcOEt, mp 216.3−217.2 °C; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.77 (t, $J$ = 7.2 Hz, 3H, $CH_2CH_3$), 1.29 (m, 1H, cyclopentyl), 1.45−1.53 (m, 5H, cyclopentyl), 1.62 (m, 1H, cyclopentyl), 2.15 (m, 1H, cyclopentyl), 2.44 (q, $J$ = 7.2 Hz, 2H, $CH_2CH_3$), 3.66−3.69 (m, 1H, cyclopentyl), 6.54 (s, 1H, CHCN), 7.54−8.15 (m, 7H, Naph), 12.85 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 400 MHz) $\delta$ 12.07 ($CH_2CH_3$), 18.29 ($CH_2CH_3$), 24.19, 24.23, 32.37, 32.52 (cyclopentyl), 38.20 (CHCN), 43.31 (cyclopentyl), 118.86 (CN), 122.49, 123.07, 125.47, 126.18, 126.83, 126.93, 128.86, 129.00, 130.06, 130.43, 133.54 (Naph, C5), 154.35 (C6), 158.86 (C2), 162.66 (C4); MS (EI) *m*/*z* 389 ($M^+$). Anal. ($C_{23}H_{23}N_3OS$) C, H, N, S.

**2-Allylthio-6-[α-cyano-(1-naphthylmethyl)]-3,4-dihydro-5-ethylpyrimidin-4(3*H*)-one (3m).** Yield 53.2%; recrystallized from MeOH, mp 195.8−197.3 °C; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 0.98 (t, $J$ = 7.5 Hz, 3H, $CH_2CH_3$), 2.49 (q, $J$ = 7.5 Hz, 2H, $CH_2CH_3$), 3.67−3.73 (m, 2H, $SCH_2$), 5.02−5.20 (m, 2H, =$CH_2$), 5.70−5.71 (m, 1H, =CH), 5.87 (s, 1H, CHCN), 7.34−8.07 (m, 7H, Naph), 12.26 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 400 MHz) $\delta$ 11.92 ($CH_2CH_3$), 18.27 ($CH_2CH_3$), 32.24 (CHCN), 38.26 ($SCH_2$), 118.07 (=$CH_2$), 118.83 (CN), 122.38, 123.03, 125.52, 126.27, 126.92, 126.97, 128.92, 129.16, 130.02, 130.39, 133.38, 133.56 (Naph, C5, =CH), 154.28 (C6), 157.99 (C2), 162.77 (C4); MS (EI) *m*/*z* 361 ($M^+$). Anal. ($C_{21}H_{19}N_3OS$) C, H, N, S.

**6-[α-Cyano-(1-naphthylmethyl)]-3,4-dihydro-5-ethyl-2-propynylthiopyrimidin-4(3*H*)-one (3n).** Yield 41.8%; recrystallized from MeOH, mp 190.4−191.1 °C; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.63 (t, $J$ = 7.2 Hz, 3H, $CH_2CH_3$), 2.36 (q, $J$ = 7.2 Hz, 2H, $CH_2CH_3$), 3.21 (s, 1H, ≡CH), 3.89−4.03 (m, 2H, $SCH_2$), 6.56 (s, 1H, CHCN), 7.54−8.30 (m, 7H, Naph), 13.04 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 400 MHz) $\delta$ 12.66 ($CH_2CH_3$), 18.23 ($CH_2CH_3$), 18.39 ($SCH_2$), 38.05 (CHCN), 73.39 (≡CH), 79.69 (≡C), 118.67 (CN), 123.02, 125.57, 126.26, 126.33, 127.06, 127.21, 128.94, 129.20, 129.99, 130.39, 133.55 (Naph, C5), 154.45 (C6), 157.26 (C2), 164.09 (C4); MS (EI) *m*/*z* 359 ($M^+$). Anal. ($C_{21}H_{17}N_3OS$) C, H, N, S.

**6-[α-Cyano-(1-naphthylmethyl)]-3,4-dihydro-5-ethyl-2-(4-nitrobenzylthio)pyrimidin-4(3*H*)-one (3o).** Yield 35.2%; recrystallized from AcOEt, mp 182.0−183.7 °C; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.10 (t, $J$ = 7.2 Hz, 3H, $CH_2CH_3$), 2.95 (q, $J$ = 7.2 Hz, 2H, $CH_2CH_3$), 4.08 (s, 2H, $SCH_2$), 5.80 (s, 1H, CHCN), 7.44−7.88 (m, 11H, Naph, Ph), 12.15 (s, 1H, NH); MS (EI) *m*/*z* 456 ($M^+$). Anal. ($C_{25}H_{20}N_4O_3S$) C, H, N, S.

**2-(4-Chlorobenzoylmethylthio)-6-[α-cyano-(1-naphthylmethyl)]-3,4-dihydro-5-ethylpyrimidin-4(3*H*)-one (3p).** Yield 32.1%; recrystallized from MeOH, mp 181.6−183.2 °C; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.96 (t, $J$ = 7.6 Hz, 3H, $CH_2CH_3$), 2.32 (q, $J$ = 7.6 Hz, 2H, $CH_2CH_3$), 3.42 (s, 2H, $SCH_2$), 4.48 (s, 1H, CHCN), 7.30−7.93 (m, 11H, Naph, Ph), 12.05 (s, 1H, NH); MS (EI) *m*/*z* 473 ($M^+$). Anal. ($C_{26}H_{20}ClN_3O_2S$) C, H, Cl, N, S.

**6-(α-Cyanobenzyl)-3,4-dihydro-5-ethyl-2-isopropylthiopyrimidin-4(3*H*)-one (3q).** Yield 47.5%; recrystallized from AcOEt, mp 140.5−141.9 °C; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.92 (t, $J$ = 7.1 Hz, 3H, $CH_2CH_3$), 1.27 (d, $J$ = 6.7 Hz, 3H, $CH_3CH$), 1.41 (d, $J$ = 6.7 Hz, 3H, $CH_3CH$), 2.47 (q, $J$ = 7.1 Hz, 2H, $CH_2CH_3$), 3.85 (sep, $J$ = 6.7 Hz, 1H, SCH), 5.88 (s, 1H, CHCN), 7.30−7.88 (m, 5H, Ph), 12.79 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 400 MHz) $\delta$ 14.36 ($CH_2CH_3$), 18.47 ($CH_2CH_3$), 22.77 ($CH_3CH$), 22.94 ($CH_3CH$), 36.39 (SCH), 36.74 (CHCN), 119.54 (CN), 122.54, 128.32 (2C), 128.87, 129.52 (2C), 134.82 (Ph, C5), 154.84 (C6), 158.96 (C2), 163.12 (C4); MS (EI) *m*/*z* 313 ($M^+$). Anal. ($C_{17}H_{19}N_3OS$) C, H, N, S.

**6-(α-Cyanobenzyl)-3,4-dihydro-5-ethyl-2-(4-nitrobenzylthio)-pyrimidin-4(3*H*)-one (3r).** Yield 39.3%; recrystallized from AcOEt, mp 89.0−90.3 °C; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.04 (t, $J$ = 7.6 Hz, 3H, $CH_2CH_3$), 2.44 (q, $J$ = 7.6 Hz, 2H, $CH_2CH_3$), 4.37 (s, 2H, $SCH_2$), 5.19 (s, 1H, CHCN), 7.17−7.84 (m, 9H, Ph, Ph), 12.41 (s, 1H, NH); MS (EI) *m*/*z* 406 ($M^+$). Anal. ($C_{21}H_{18}N_4O_3S$) C, H, N, S.

**6-(α-Cyano-2,6-dichlorobenzyl)-3,4-dihydro-5-ethyl-2-(4-nitrobenzylthio)pyrimidin-4(3*H*)-one (3s).** Yield 31.0%; recrystallized from AcOEt, mp 109.9−111.1 °C; $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 1.12 (t, $J$ = 7.2 Hz, 3H, $CH_2CH_3$), 2.32 (q, $J$ = 7.2 Hz, 2H, $CH_2CH_3$), 4.49 (s, 2H, $SCH_2$), 6.47 (s, 1H, CHCN), 7.47−9.84 (m, 7H, Ar), 13.00 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 400 MHz) $\delta$ 11.99 ($CH_2CH_3$), 12.10 (CHCN), 18.88 ($CH_2CH_3$), 32.60 ($SCH_2$), 116.97 (CN), 119.78 (C5), 123.85 (2C), 130.03, 130.13 (2C), 130.29 (2C), 131.46, 135.70, 135.76, 146.59, 147.02 (Ar), 148.58 (C6), 159.93 (C2), 164.08 (C4); MS (EI) *m*/*z* 474 ($M^+$). Anal. ($C_{21}H_{16}Cl_2N_4O_3S$) C, H, Cl, N, S.

**6-[α-Cyano-(1-naphthylmethyl)]-2-cyclopentylthio-3,4-dihydro-5-isopropylpyrimidin-4(3*H*)-one (3t).** Yield 47.3%; recrystallized from AcOEt, mp 172.6−173.8 °C; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.19 (d, $J$ = 7.2 Hz, 6H, $CH(CH_3)_2$), 1.42−1.48 (m, 4H, cyclopentyl), 1.61−1.63 (m, 2H, cyclopentyl), 1.86−1.90 (m, 2H, cyclopentyl), 3.11 (sep, $J$ = 7.2 Hz, 1H, $CH(CH_3)_2$), 3.47 (m, 1H, cyclopentyl), 5.94 (s, 1H, CHCN), 7.23−7.83 (m, 7H, Naph), 12.16 (s, 1H, NH); $^{13}$C NMR ($CDCl_3$, 400 MHz) $\delta$ 19.78 (2C, $CH(CH_3)_2$), 21.68 ($CH(CH_3)_2$), 24.61, 24.74 (cyclopentyl), 29.63 (CHCN), 33.04

(2C, cyclopentyl), 43.67 (cyclopentyl), 115.36 (CN), 122.67, 124.69, 126.57, 127.55, 128.13, 129.07, 129.61, 129.82, 130.24, 131.46, 135.17 (Naph, C5), 159.08 (C6), 159.55 (C2), 165.96 (C4); MS (EI) *m*/*z* 403 ($M^+$). Anal. ($C_{24}H_{25}N_3OS$) C, H, N, S.

**6-[α-Cyano-(1-naphthylmethyl)]-3,4-dihydro-5-isopropyl-2-(4-methoxybenzylthio)pyrimidin-4(3*H*)-one (3u).** Yield 40.1%; recrystallized from MeOH, mp 104.3−105.6 °C; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.18 (d, $J$ = 7.3 Hz, 6H, $CH(CH_3)_2$), 2.49 (sep, $J$ = 7.3 Hz, 1H, $CH(CH_3)_2$), 3.43 (s, 3H, $OCH_3$), 4.51 (s, 2H, $SCH_2$), 5.91 (s, 1H, CHCN), 7.20−7.87 (m, 11H, Ar), 12.69 (s, 1H, NH); MS (EI) *m*/*z* 455 ($M^+$). Anal. ($C_{27}H_{25}N_3O_2S$) C, H, N, S.

**6-(α-Cyanobenzyl)-3,4-dihydro-5-isopropyl-2-(4-methoxybenzylthio)pyrimidin-4(3*H*)-one (3v).** Yield 33.7%; recrystallized from MeOH, mp 69.0−70.2 °C; $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 1.16 (d, $J$ = 7.2 Hz, 6H, $CH(CH_3)_2$), 2.48 (sep, $J$ = 7.3 Hz, 1H, $CH(CH_3)_2$), 3.09 (s, 3H, $OCH_3$), 4.42 (s, 2H, $SCH_2$), 5.98 (s, 1H, CHCN), 7.07−7.87 (m, 9H, Ar), 12.75 (s, 1H, NH); MS (EI) *m*/*z* 405 ($M^+$). Anal. ($C_{23}H_{23}N_3O_2S$) C, H, N, S.

**6-(α-Cyano-2,6-dichlorobenzyl)-3,4-dihydro-5-isopropyl-2-(4-methoxybenzylthio)pyrimidin-4(3*H*)-one (3w).** Yield 31.4%; recrystallized from MeOH, mp 64.0−65.2 °C; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.20 (d, $J$ = 7.0 Hz, 6H, $CH(CH_3)_2$), 2.50 (sep, $J$ = 7.0 Hz, 1H, $CH(CH_3)_2$), 3.41 (s, 3H, $OCH_3$), 4.03 (s, 2H, $SCH_2$), 6.05 (s, 1H, CHCN), 7.29−7.42 (m, 7H, Ar), 11.05 (s, 1H, NH); MS (EI) *m*/*z* 473 ($M^+$). Anal. ($C_{23}H_{21}Cl_2N_3O_2S$) C, H, Cl, N, S.

**General Procedure for the Synthesis of 5-Alkyl-2-alkylthio-6-arylcarbonyl-3,4-dihydropyrimidin-4(3*H*)-ones 4a−m.** 5-Alkyl-2-alkylthio-6-(α-cyanoarylmethyl)-3,4-dihydropyrimidin-4(3*H*)-ones **3b**, **3d**, **3g**, **3j**,**k**, **3m**, **3t**, and **3x**−**ac** (2 mmol) was dissolved in anhydrous DMF (50 mL) under nitrogen atmosphere. The solution was cooled to −10 °C, and NaH (0.10 g, 2.4 mmol) (60% in paraffin) was added portionwise. The resulting mixture was stirred for 0.5 h, warmed to room temperature, and then air was passed through the reaction mixture for 6−12 h. The resulting solution was neutralized with acetic acid, concentrated in vacuo, and added to water (100 mL). A precipitate which formed was filtered off, washed with water, dried, and recrystallized from AcOEt.

**3,4-Dihydro-2-ethylthio-6-(1-naphthoyl)pyrimidin-4(3*H*)-one (4a).** Yield 82.5%; mp 222.0−223.2 °C; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.95 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.75 (sep, $J$ = 7.2 Hz, 2H, $SCH_2$), 6.57 (s, 1H, CH), 7.60−8.26 (m, 7H, Naph), 13.09 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 400 MHz) $\delta$ 14.14 ($CH_3$), 24.33 ($CH_2$), 110.26 (C5), 124.46, 125.02, 125.43, 127.75, 128.57, 130.21, 130.33, 132.61, 133.07, 133.13 (Naph), 154.71 (C6), 158.70 (C2), 162.95 (C4), 195.00 (C═O); MS (EI) *m*/*z* 310 ($M^+$). Anal. ($C_{17}H_{14}N_2O_2S$) C, H, N, S.

**2-Cyclopentylthio-3,4-dihydro-6-(1-naphthoyl)pyrimidin-4(3*H*)-one (4b).** Yield 86.1%; mp 186.4−187.4 °C; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$ 1.27−1.30 (m, 4H, cyclopentyl), 1.47 (m, 2H, cyclopentyl), 1.61 (m, 2H, cyclopentyl), 3.31 (m, 1H, cyclopentyl), 6.61 (s, 1H, CH), 7.60−8.18 (m, 7H, Naph), 13.09 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 400 MHz) $\delta$ 24.00 (2C), 32.20 (2C), 43.32 (cyclopentyl), 109.71 (C5), 124.51, 125.04, 126.39, 127.60, 128.51, 129.67, 130.14, 132.25, 133.01, 133.60 (Naph), 155.02 (C6), 158.39 (C2), 163.38 (C4), 195.37 (C═O); MS (EI) *m*/*z* 350 ($M^+$). Anal. ($C_{20}H_{18}N_2O_2S$) C, H, N, S.

**2-Benzoylmethylthio-3,4-dihydro-6-(1-naphthoyl)pyrimidin-4(3*H*)-one (4c).** Yield 30.7%; mp 183.2−183.7 °C; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$ 3.86 (s, 2H, $SCH_2$), 6.97 (CH), 7.42−8.08 (m, 12H, Naph, Ph), 13.15 (s, 1H, NH); MS (EI) *m*/*z* 400 ($M^+$). Anal. ($C_{23}H_{16}N_2O_3S$) C, H, N, S.

**6-Benzoyl-3,4-dihydro-2-ethylthiopyrimidin-4(3*H*)-one (4d).** Yield 90.3%; mp 173.2−174.5 °C; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$ 1.23 (t, $J$ = 7.3 Hz, 3H, $CH_3$), 3.05 (q, $J$ = 7.3 Hz, 2H, $SCH_2$), 6.46 (s, 1H, CH), 7.47−7.97 (m, 5H, Ph), 13.11 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 400 MHz) $\delta$ 14.38 ($CH_3$), 24.39 ($CH_2$), 109.76 (C5), 128.42 (2C), 130.14, 133.77, 134.69 (Ph), 154.75 (C6), 159.06 (C2), 162.38 (C4), 192.17 (C═O); MS (EI) *m*/*z* 260 ($M^+$). Anal. ($C_{13}H_{12}N_2O_2S$) C, H, N, S.

**6-Benzoyl-3,4-dihydro-2-isopropylthio-5-methylpyrimidin-4(3*H*)-one (4e).** Yield 88.7%; mp 121.1−122.7 °C; $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 1.22 (d, $J$ = 7.0 Hz, 6H, $(CH_3)_2CH$), 1.78 (s, 3H, $CH_3$), 3.67 (sep, $J$ = 6.8 Hz, 1H, SCH), 7.40−7.88 (m, 5H, Ph), 12.91 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 400 MHz) $\delta$ 10.51 ($CH_3$), 22.30 ($CH_3$), 22.20, 22.39 ($CH(CH_3)_2$), 35.75 (SCH), 128.91, 129.01, 129.51, 129.67, 134.24, 134.31, 134.39 (Ph, C5), 155.93 (C6), 158.70 (C2), 162.87 (C4), 193.47 (C═O); MS (EI) *m*/*z* 288 ($M^+$). Anal. ($C_{15}H_{16}N_2O_2S$) C, H, N, S.

**3,4-Dihydro-5-methyl-6-(1-naphthoyl)-2-propynylthiopyrimidin-4(3*H*)-one (4f).** Yield 70.6%; mp 249.0−250.7 °C; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$ 1.86 (s, 3H, $CH_3$), 3.18 (s, 1H, ≡CH), 3.98 (m, 2H, $SCH_2$), 7.50−8.29 (m, 7H, Naph), 13.11 (s, 1H, NH); MS (EI) *m*/*z* 334 ($M^+$). Anal. ($C_{19}H_{14}N_2O_2S$) C, H, N, S.

**3,4-Dihydro-5-ethyl-2-ethylthio-6-(1-naphthoyl)pyrimidin-4(3*H*)-one (4g).** Yield 87.9%; mp 171.0−172.5 °C; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$ 1.01 (d, $J$ = 6.9 Hz, 6H, 2×$CH_3$), 2.32 (q, $J$ = 6.9 Hz, 2H, $CH_2CH_3$), 2.83 (q, $J$ = 6.9 Hz, 2H, $SCH_2$), 7.60−8.87 (m, 7H, Naph), 12.98 (s, 1H, NH); MS (EI) *m*/*z* 338 ($M^+$). Anal. ($C_{19}H_{18}N_2O_2S$) C, H, N, S.

**3,4-Dihydro-5-ethyl-2-isopropylthio-6-(1-naphthoyl)pyrimidin-4(3*H*)-one (4h).** Yield 85.3%; mp 141.6−142.3 °C; $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 0.94 (t, $J$ = 7.2 Hz, 3H, $CH_2CH_3$), 1.21 (d, $J$ = 6.8 Hz, 6H, $(CH_3)_2CH$), 2.21 (q, $J$ = 7.2 Hz, 2H, $CH_2$-$CH_3$), 3.66 (sep, $J$ = 6.8 Hz, 1H, SCH), 6.68−7.87 (m, 7H, Naph), 12.93 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 400 MHz) $\delta$ 13.16 ($CH_3$-$CH_2$), 18.47 ($CH_3CH_2$), 22.34 (2C, $CH(CH_3)_2$), 35.69 (SCH), 127.84, 128.85, 129.27, 129.66, 129.89, 130.15, 134.30, 134.44 (Naph, C5), 156.08 (C6), 158.97 (C2), 162.40 (C4), 193.34 (C═O); MS (EI) *m*/*z* 352 ($M^+$). Anal. ($C_{20}H_{20}N_2O_2S$) C, H, N, S.

**2-Allylthio-3,4-dihydro-5-ethyl-6-(1-naphthoyl)pyrimidin-4(3*H*)-one (4i).** Yield 80.4%; mp 133.1−134.4 °C; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.14 (t, $J$ = 7.4 Hz, 3H, $CH_2CH_3$), 2.51 (q, $J$ = 7.4 Hz, 2H, $CH_2CH_3$), 3.62 (d, $J$ = 7.0 Hz, 2H, $SCH_2$), 4.97−5.03 (m, 2H, ═$CH_2$), 5.67−5.72 (m, 1H, ═CH), 7.48−9.15 (m, 7H, Naph), 11.34 (s, 1H, NH); MS (EI) *m*/*z* 350 ($M^+$). Anal. ($C_{20}H_{18}N_2O_2S$) C, H, N, S.

**2-Benzylthio-3,4-dihydro-5-ethyl-6-(1-naphthoyl)pyrimidin-4(3*H*)-one (4j).** Yield 91.3%; mp 219.9−221.3 °C; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$ 1.02 (t, $J$ = 7.2 Hz, 3H, $CH_2CH_3$), 2.35 (q, $J$ = 7.2 Hz, 2H, $CH_2CH_3$), 4.09 (s, 2H, $SCH_2$), 7.02−8.85 (m, 12H, Naph, Ph), 13.01 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 400 MHz) $\delta$ 12.32 ($CH_2CH_3$), 16.16 ($CH_2CH_3$), 33.24 ($SCH_2$), 127.40 (2C), 127.88 (3C), 128.44 (3C), 128.83 (3C), 130.03 (3C), 134.16, 136.17 (Ar), 145.45 (C5), 148.03 (C6), 158.39 (C2), 164.33 (C4), 191.98 (C═O); MS (EI) *m*/*z* 400 ($M^+$). Anal. ($C_{24}H_{20}N_2O_2S$) C, H, N, S.

**2-Benzylthio-3,4-dihydro-5-ethyl-6-(2-naphthoyl)pyrimidin-4(3*H*)-one (4k).** Yield 90.7%; mp 200.0−201.1 °C; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$ 1.03 (t, $J$ = 7.4 Hz, 3H, $CH_2CH_3$), 2.34 (q, $J$ = 7.4 Hz, 2H, $CH_2CH_3$), 3.84 (s, 2H, $SCH_2$), 7.17−8.92 (m, 12H, Naph, Ph), 13.11 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 400 MHz) $\delta$ 12.32 ($CH_2CH_3$), 16.16 ($CH_2CH_3$), 33.23 ($SCH_2$), 127.41 (2C), 127.85 (3C), 128.48 (3C), 128.85 (3C), 130.04 (3C), 134.15, 136.17 (Ar), 145.46 (C5), 148.04 (C6), 158.35 (C2), 164.32 (C4), 191.96 (C═O); MS (EI) *m*/*z* 400 ($M^+$). Anal. ($C_{24}H_{20}N_2O_2S$) C, H, N, S.

**6-Benzoyl-2-cyclopentylthio-3,4-dihydro-5-ethylpyrimidin-4(3*H*)-one (4l).** Yield 84.3%; mp 162.0−163.3 °C; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.95 (t, $J$ = 7.1 Hz, 3H, $CH_2CH_3$), 1.46 (m, 4H, cyclopentyl), 1.58 (m, 2H, cyclopentyl), 1.93 (m, 2H, cyclopentyl), 2.21 (q, $J$ = 7.1 Hz, 2H, $CH_2CH_3$), 3.74−3.75 (m, 1H, cyclopentyl), 7.55−7.89 (m, 5H, Ph), 12.95 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 400 MHz) $\delta$ 13.18 ($CH_2CH_3$), 18.46 ($CH_2CH_3$), 24.24 (2C, cyclopentyl), 32.56 (2C, cyclopentyl), 43.08 (cyclopentyl), 123.12, 128.83 (2C), 129.69 (2C), 134.29, 134.51 (Ph, C5), 156.09 (C6), 159.53 (C2), 162.45 (C4), 193.41 (C═O); MS (EI) *m*/*z* 328 ($M^+$). Anal. ($C_{18}H_{20}N_2O_2S$) C, H, N, S.

**2-Cyclopentylthio-3,4-dihydro-5-isopropyl-6-(1-naphthoyl)pyrimidin-4(3*H*)-one (4m).** Yield 87.6%; mp 155.2−157.0 °C; $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 1.18 (d, $J$ = 7.1 Hz, 6H, $CH(CH_3)_2$),

1.47 (m, 4H, cyclopentyl), 1.61−1.62 (m, 2H, cyclopentyl), 1.93 (m, 2H, cyclopentyl), 2.97 (sep, $J = 7.1$ Hz, 1H, $CH(CH_3)_2$), 3.39−3.42 (m, 1H, cyclopentyl), 7.52−8.13 (m, 7H, Naph), 13.06 (s, 1H, NH); $^{13}C$ NMR (DMSO-$d_6$, 400 MHz) $\delta$ 19.89 (2C, $CH(CH_3)_2$), 21.99 ($CH(CH_3)_2$), 24.60, 24.76 (cyclopentyl), 33.16 (2C, cyclopentyl), 43.61 (cyclopentyl), 122.67, 124.71, 126.55, 127.58, 128.12, 129.05, 129.59, 129.78, 130.21, 131.44, 135.18 (Naph, C5), 159.03 (C6), 159.39 (C2), 164.99 (C4), 194.00 (C═O); MS (EI) *m*/*z* 392 ($M^+$). Anal. ($C_{23}H_{24}N_2O_2S$) C, H, N, S.

**Methods. X-ray Crystallography of Compounds 3k and 4b.** Single crystals of **3k** and **4b** suitable for X-ray diffraction analysis were obtained by recrystallization from methanol and ethyl acetate, respectively. All measurements were made on an Enraf-Nonius CAD-4 diffractometer.

Data were collected using CAD-4 Software (Enraf−Nonius, Delft, The Netherlands, 1994). Cell were refined with CAD-4, and data reduction was performed with XCAD4 (Harms & Wocadlo, 1994). The structure was solved by SHELX-S97[21] and was refined using SHELX-L97.[22] Software used to prepare molecular graphics was ORTEP-3 for Windows (Version 1.05; Farrugia, 1997).

The data for **3k** were as follows: $C_{21}H_{21}N_3OS$, $M_r$ 363.47, $a = 10.822(3)$ Å, $b = 15.375(3)$ Å, $c = 12.061(4)$ Å, $\beta = 105.51(3)°$, $V = 1933.7(9)$ Å$^3$, $Z = 4$, space group *P21*/*n*, monoclinic, $F(000) = 768$, $d_c = 1.248$ mg/m$^3$, $\mu = 0.18$ mm$^{-1}$, $\lambda = 0.71073$ Å, $T = 295(2)$ K. Of a total of 4116 reflections were measured, 3476 were independent with $R = 0.044$, $wR(F^2) = 0.139$ [$I > 2\sigma(I)$], and $S = 1.01$. Parameters refined 343, $(\Delta\rho)_{max} = 0.38$ e Å$^{-3}$, $(\Delta\rho)_{min} = -0.18$ e Å$^{-3}$, $(\Delta/\sigma)_{max} < 0.001$, extinction coefficient = 0.0036(11).

The data for **4b** were as follows: $C_{20}H_{18}N_2O_2S$, $M_r$ 350.42, $a = 11.920(2)$ Å, $b = 10.312(3)$ Å, $c = 14.855(4)$ Å, $\beta = 108.43(2)°$, $V = 1732.3(7)$ Å$^3$, $Z = 4$, space group *P21*/*n*, monoclinic, $F(000) = 736$, $d_c = 1.344$ mg/m$^3$, $\mu = 0.20$ mm$^{-1}$, $\lambda = 0.71073$ Å, $T = 295(2)$ K. Of a total of 3499 reflections were measured, 3109 were independent with $R = 0.039$, $wR(F^2) = 0.117$ [$I > 2\sigma(I)$], and $S = 1.01$. Parameters refined 231, $(\Delta\rho)_{max} = 0.24$ e Å$^{-3}$, $(\Delta\rho)_{min} = -0.20$ e Å$^{-3}$, $(\Delta/\sigma)_{max} < 0.001$, extinction coefficient = 0.0037(10).

**Biological Activity.** The anti-HIV activity and cytotoxicity were evaluated against wild type HIV-1 strain $III_B$ in MT-4 cells using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method.[23] Briefly, virus stocks were titrated in MT-4 cells and expressed as the 50% cell culture infective dose ($CCID_{50}$). MT-4 cells were suspended in culture medium at $1 \times 10^5$ cells/mL and infected with HIV at a multiplicity of infection of 0.02. Immediately after viral infection, 100 $\mu$L of the cell suspension was placed in each well of a flat-bottomed microtiter tray containing various concentrations of the test compounds. The test compounds were dissolved in DMSO at 50 mM or higher. After 4 days of incubation at 37 °C, the number of viable cells was determined using the MTT method. Compounds were tested in parallel for cytotoxic effects in uninfected MT-4 cells.

Peripheral blood mononuclear cells (PBMCs) from healthy donors were isolated by density centrifugation (Lymphoprep; Nycomed Pharma, AS Diagnostics, Oslo, Norway) and stimulated with phytohemagglutin (PHA) (Sigma Chemical Co., Bornem, Belgium) for 3 days. The activated cells (PHA-stimulated blasts) were washed with PBS, and viral infections were done as described by the AIDS clinical trial group protocols.[24] Briefly, PBMCs ($2 \times 10^5$/200 $\mu$L) were plated in the presence of serial dilutions of the test compound and were infected with HIV stocks at 1000 $CCID_{50}$ per mL. At day 4 postinfection, 125 $\mu$L of the supernatant of the infected cultures was removed and replaced with 150 $\mu$L of fresh medium containing the test compound at the appropriate concentration. At 7 days after plating the cells, p24 antigen was detected in the culture supernatant by an enzyme-linked immunosorbent assay (NEN, Paris, France).

**Computational Details.** All calculations and manipulations were performed using Autodock 3.0.5[25] and Sybyl 6.7,[26] running on Silicon Graphics O2 R10000 workstations.

Three-dimensional coordinates of the HIV-1 RT/MKC-442 (emivirine) complex (Brookhaven Protein Data Bank entry 1RT1) were used as the input structure for docking calculations. For this aim, all cocrystallized water molecules and the ligand were deleted, all hydrogens were added, and Amber95 charges were loaded using the appropriate tool in the Biopolymer module of Sybyl and submitted to minimization with the steepest descent methods and conjugated gradients methods (Tripos force field) to an energy gradient of 0.05 kcal/(mol·Å). The structure of the new *S*-DABO derivative **3g** was built using the Sybyl Sketcher model and fully minimized with the Powell method (MMFF94 force field) to an energy gradient of 0.05 kcal/(mol·Å).

Docking simulations were performed with the program AutoDock 3.0.5. Grids of molecular interactions were calculated in a cubic box (size, 25.125 Å; grid spacing: 0.375 Å). Docking was performed 100 times using the Lamarckian genetic algorithm with random starting position and conformation, standard parameters, and a maximum of 250 000 energy evaluations. The 10 final docked conformations were ranked according to their binding free energy.

**Acknowledgment.** We are grateful to the National Natural Science Foundation of China (No. 30672536) for the financial support of this research.

**Supporting Information Available:** Elemental analysis data for the title compounds and X-ray crystallographic information for compounds **3k** and **4b**. This material is available free of charge via the Internet at http://pubs.acs.org.

## References

(1) Botta, M.; Artico, M.; Massa, S.; Gambacorta, A.; Marongiu, M. E.; Pani, A.; La Colla, P. Synthesis, Antimicrobial and Antiviral Activities of Isotrimethoprim and Some Related Derivatives. *Eur. J. Med. Chem.* **1992**, *27*, 251−257.

(2) Artico, M.; Massa, S.; Mai, A.; Marongiu, M. E.; Piras, G.; Tramontano, E.; La Colla, P. 3,4-Dihydro-2-alkoxy-6-benzyl-4-oxopyrimidines (DABOs): a New Class of Specific Inhibitors of Human Immunodeficiency Virus Type 1. *Antiviral Chem. Chemother.* **1993**, *4*, 361−368.

(3) Tramontano, E.; Marongiu, M. E.; De Montis, A.; Loi, A. G.; Artico, M.; Massa, S.; Mai, A.; La Colla, P. Characterization of the Anti-HIV-1 Activity of 3,4-Dihydro-2-alkoxy-6-benzyl-4-oxopyrimidines (DABOs), New Non-Nucleoside Reverse Transcriptase Inhibitors. *Microbiologica* **1994**, *17*, 269−279.

(4) Mai, A.; Artico, M.; Sbardella, G.; Massa, S.; Loi, A. G.; Tramontano, E.; Scano, P.; La Colla, P. Synthesis and Anti-HIV-1 Activity of Thio Analogues of Dihydroalkoxybenzyloxopyrimidines. *J. Med. Chem.* **1995**, *38*, 3258−3263.

(5) Massa, S.; Mai, A.; Artico, M.; Sbardella, G.; Tramontano, E.; Loi, A. G.; Scano, P.; La Colla, P. Synthesis and Antiviral Activity of New 3,4-Dihydro-2-alkoxy-6-benzyl-4-oxopyrimidines (DABOs), Specific Inhibitors of Human Immunodeficiency Virus Type-1. *Antiviral Chem. Chemother.* **1996**, *6*, 1−8.

(6) Ettorre, A.; Mai, A.; Artico, M.; Massa, S.; De Montis, A.; La Colla, P. 6-(3-Methylbenzyl)-2-(2-methylpropyl)thio-4(3*H*)-pyrimidinone (DABO 622). *Acta. Crystallogr.* **1996**, *C52*, 2115−2117.

(7) Mai, A.; Artico, M.; Sbardella, G.; Quartarone, S.; Massa, S.; Loi, A. G.; De Montis, A.; Scintu, F.; Putzolu, M.; La Colla, P. Dihydro-(alkylthio)(naphthylmethyl)oxopyrimidines: Novel Nonnucleoside Reverse Transcriptase Inhibitors of the S-DABO Series. *J. Med. Chem.* **1997**, *40*, 1447−1454.

(8) Vig, R.; Mao, C.; Venkatachalam, T. K.; Tuel-Ahlgren, L.; Sudbeck, E. A.; Uckun, F. M. 5-Alkyl-2-[(methylthiomethyl)thio]-6-(benzyl)-pyrimidin-4-(1*H*)-ones as Potent Non-Nucleoside Reverse Transcriptase Inhibitors of *S*-DABO Series. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1461−1466.

(9) Mai, A.; Artico, M.; Sbardella, G.; Massa, S.; Novellino, E.; Greco, G.; Loi, A. G.; Tramontano, E.; Marongiu, M. E.; La Colla, P. 5-Alkyl-2-(alkylthio)-6-(2,6-dihalophenylmethyl)-3,4-dihydropyrimidin-4( 3*H*)-ones: Novel Potent and Selective Dihydro-alkoxybenzyl-oxopyrimidine Derivatives. *J. Med. Chem.* **1999**, *42*, 619−627.

(10) Artico, M.; Mai, A.; Sbardella, G.; Massa, S.; La Colla, P. Does the 2-Methylthiomethyl Substituent Really Confer High Anti-HIV-1 Activity to *S*-DABOs? *Med. Chem. Res.* **2000**, *10*, 30−39.

(11) Mai, A.; Sbardella, G.; Artico, M.; Ragno, R.; Massa, S.; Novellino, E.; Greco, G.; Lavecchia, A.; Musiu, C.; La Colla, M.; Murgioni, C.; La Colla, P.; Loddo, R. Structure-based Design, Synthesis, and

Biological Evaluation of Conformationally Restricted Novel 2-Alkylthio-6-[1-(2,6-difluorophenyl)alkyl]-3,4-dihydro-5-alkylpyrimidin-4(3*H*)-ones as Non-Nucleoside Inhibitors of HIV-1 Reverse Transcriptase. *J. Med. Chem.* **2001**, *44*, 2544−2554.

(12) Quaglia, M.; Mai, A.; Sbardella, G.; Artico, M.; Ragno, R.; Massa, S.; del Piano, D.; Setzu, G.; Doratiotto, S.; Cotichini, V. Chiral Resolution and Molecular Modeling Investigation of Rac-2-cyclopentylthio-6-[1-(2,6-difluorophenyl)ethyl]-3,4-dihydro-5-methylpyrimidin-4-(3*H*)-one (MC-1047), a Potent Anti-HIV-1 Reverse Transcriptase Agent of the DABO Class. *Chirality* **2001**, *13*, 75−80.

(13) Sbardella, G.; Mai, A.; Artico, M.; Chimenti, P.; Maasa, S.; Loddo, R.; Marongiu, M. E.; La Colla, P.; and Pani, A. Structure Activity Relationship Studies on New DABOs: Effect of Substitutions at Pyrimidine C-5 and C-6 Positions on Anti-HIV-1 Activity. *Antiviral Chem. Chemother.* **2001**, *12*, 37−50.

(14) Marongiu, M. E.; Pani, A.; Musiu, C.; La Colla, P.; Mai, A.; Sbardella, G.; Massa, S.; Artico, M. 3,4-Dihydro-2-alkoxy-6-benzyloxopyrimidines (DABOs): Development of a Potent Class of Non-Nucleoside Reverse Transcriptase Inhibitors. *Recent Res. Dev. Med. Chem.* **2002**, *1*, 65−92.

(15) Artico, M. Selected Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs): the DABOs Family. *Drugs Future* **2002**, *27*, 159−175.

(16) Ragno, R.; Mai, A.; Sbardella, G.; Artico, M.; Massa, S.; Musiu, C.; Mura, M.; Marturana, F.; Cadeddu, A.; La Colla, P. Computer-Aided Design, Synthesis, and Anti-HIV-1 Activity in Vitro of 2-Alkylamino-6-[1-(2,6-difluorophenyl)alkyl]-3,4-dihydro-5-alkylpyrimidin-4-(3*H*)-ones as Novel Potent Non-Nucleoside Reverse Transcriptase Inhibitors, Also Active Against the Y181C Variant. *J. Med. Chem.* **2004**, *47*, 928−934.

(17) Mai, A.; Artico, M.; Ragno, R.; Sbardella, G.; Massa, S.; Musiu, C.; Mura, M.; Marturana, F.; Cadeddu, A.; Maga, G.; La Colla, P. 5-Alkyl-2-alkylamino-6-(2,6-difluorophenylalky)-3,4-dihydropyrimidin-4( 3*H*)-ones, a New Series of Potent, Broad-Spectrum Non-Nucleoside Reverse Transcriptase Inhibitors Belonging to the DABO Family. *Bioorg. Med. Chem.* **2005**, *13*, 2065−2077.

(18) Manetti, F.; A. Esté, J.; Clotet-Codina, I.; Armand-Ugón, M.; Maga, G.; Crespan, E.; Cancio, R.; Mugnaini, C.; Bernardini, C.; Togninelli, A.; Carmi, C.; Alongi, M.; Petricci, E.; Massa, S.; Corelli, F.; Botta, M. Parallel Solution-Phase and Microwave-Assisted Synthesis of New *S*-DABO Derivatives Endowed with Subnanomolar Anti-HIV-1 Activity. *J. Med. Chem.* **2005**, *48*, 8000−8008.

(19) He, Y. P.; Chen, F. E.; Sun, G. F.; Wang, Y. P.; De Clercq, E.; Balzarini, J.; Pannecouque, C. 5-Alkyl-2-[(aryl and alkyloxylcarbonylmethyl)thio]-6-(1-naphthylmethyl) pyrimidin-4(3H)-ones as an Unique HIV Reverse Transcriptase Inhibitors of *S*-DABO Series. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3173−3176.

(20) Koroniak, H.; Jankowski, A.; Krasnowski, M. Facile Large Scale Synthesis of 5-Alkyluracils. *Org. Prep. Proc. Int.* **1993**, *25*, 563−568.

(21) Sheldrick, G. M. *Program for the Solution of Crystal Structures*; University of Göttingen: Göttingen, Germany, 1997.

(22) Sheldrick, G. M. *Program for the Refinement of Crystal Structures*; University of Göttingen: Göttingen, Germany, 1997.

(23) Pauwels, R.; Balzarini, J.; Baba, M.; Snoeck, R.; Schols, D.; Herdewijn, P.; Desmyter, J.; De Clercq, E. Rapid and Automated Tetrazolium-Based Colorimetric Assay for the Detection of Anti-HIV Compounds. *J. Virol. Methods* **1988**, *20*, 309−321.

(24) Japour, A. J.; Mayers, D. L.; Johnson, V. A.; Kuritzkes, D. R.; Beckett, L. A.; Arduino, J. M.; Lane, J.; Black, R. L.; Reichelderfer, P. S.; D'Aquila, R. T.; Crumpacker, C. S. Standardized Peripheral Blood Mononuclear Cell Culture Assay for Determination of Drug Susceptibilities of Clinical Human Immunodeficiency Virus Type 1 Isolates. *Antimicrob. Agents Chemother.* **1993**, *37*, 1095−1101.

(25) Goodsell, D. S.; Morris, G. M.; Olson, A. J. Automated Docking of Flexible Ligands: Applications of AutoDock. *J. Mol. Recognit.* **1996**, *9*, 1−5.

(26) *Sybyl Molecular Modelling System*, version 6.7; Tripos, Inc., St. Louis, MO.

JM061167R